REMARKS

Claims 31-33, 39-43 and 48 are pending. It is noted that the Office Action Summary mistakenly omits pending claim 48, and appropriate correction by the Examiner is respectfully requested.

Claims 50-62 have been added and therefore are pending in the present application. Claims 50-62 depend from claim 31, and are supported by the specification and claims as originally filed. In particular, claims 50-55 depend from claim 31, and are supported by, e.g., original claim 1. Claims 56-62 are supported, e.g., by the specification at page 4, lines 26-40.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance. Reconsideration of the application in view of the above amendments and the following remarks is requested.

I. Specification

The Examiner states that the substitute sequence listing filed on January 23, 2003 is confusing as it is not clear why the total number of sequences have increased.

SEQ ID NO:3 was added and intended to identify only the mature peptide encoded by SEQ ID NO:1. However, upon review, it appears that SEQ ID NO: contains amino acids in addition to the mature peptide (namely, amino acids corresponding to positions negative 1 to negative 20). A new sequence listing is submitted herewith, deleting SEQ ID NO:3.

II. The Rejection of Claim 32 under 35 U.S.C. 112

Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as indefinite. The Examiner states that the substitute sequence listing renders the claims indefinite. The Examiner states that "It appears that applicant replaced the original SEQ ID NO:2 with a substitute wherein Q132 is occupied by a glutamine in substitute sequence listing."

Applicants note that the substitution recited in claim 32 is Q153S not Q132, as stated by the Examiner. (The amino acid at position 132 of SEQ ID NO:2 is a valine not a glutamine.) Moreover, the amino acid occupying position 153 in SEQ ID NO:2 is identified as a glutamine, which is correctly abbreviated by a "Q" in claim 32. Thus, claim 32 is not indefinite.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 112. Applicants respectfully request reconsideration and withdrawal of the rejection.

III. The Rejection of Claims 31-33, 39-43 and 48 under 35 U.S.C. 103

The rejection of claims 31-33, 39-43 and 48 under 35 U.S.C. 103 as being unpatentable over Christianson in view of Matsuura and Svendsen. In maintaining the rejection, the Examiner states:

> [Applicants'] arguments were fully considered but was found unpersuasive for the following reasons: with respect to applicant's **first** argument the examiner would like to indicate that had any of the cited art alone, taught the variants of this invention said art would have been anticipatory to this invention.
>
> In response to applicant's **second** argument the examiner agrees with the applicant that the cited art teaches about variants of bacterial amylase variants and bacterial related amylases have relatively low sequence homology to fungal related amylases and Svendsen exploited regions of low homology to fungal amylases for variant preparation. Nevertheless, the examiner maintains that based on the ample knowledge for various domains of conserved/non-conserved homology of amylases in the prior art, to one of ordinary skill in the art, preparation of variants of any amylase with predicted properties, is obvious and does not require undue experimentation.
>
> This conclusion is particularly supported by the fact that structural characterization of amylases in the prior art are not merely based on amino acid homology (identity) but also based on physical properties of constituent amino acids of said enzymes. Applicant is respectfully requested to consider Holm et al. [citation omitted] which aligns various amylases from fungal (Taka-amylase), mammalian and bacterial sources using physical properties of constituent amino acids as a basis for alignment and points out domains A and C (see figure 1) of highly structural similarity around the catalytic site and secondary structure elements, as well as domains of very little amino acid homology or similarity in beta strand arrangements (domain b), to be exploited for variant preparation with predicted activities.

(Emphasis in original.)

The Examiner then alleges that Holm indicates that the three dimensional model of *B. stearothermophilus* (bacterial) alpha amylase is based on or modeled after a fungal source, i.e., Taka-amylase, and this "fact about Taka amylase is also indicated in Svendsen (see page 2)." The Examiner concludes that the criteria for aligning the structures of various amylases is not merely amino acid homology, but other factors such as the physical properties of constituent amino acids, mostly based on/modeled after the three-dimensional structure of fungal amylases.

This rejection is respectfully traversed as the Examiner has clearly failed to establish a *prima facie* case of obviousness. Moreover, the Examiner has clearly failed to give proper consideration, if any, to Svendsen et al's unambiguous teaching away from the present invention.

First, it is unclear what the Examiner' intends by the statement:

> had any of the cited art alone, taught the variants of this invention said art would have been anticipatory to this invention.

For the purpose of responding, however, Applicants assume that the Examiner is implying that art cited for the obviousness rejection is relevant because, although it is directed to (1) completely different enzymes (proteases of Christianson), (2) distantly related enzymes (bacterial alpha-amylases of Svendsen) and (3) fungal enzymes, but unrelated variants (the fungal variants of Matsuura), that these references would nevertheless easily be anticipatory if the modifications were found in the references.

As previously stated, the relevance of the Examiner's statement to the arguments presented in the last response is not apparent. Moreover, the Examiner's statement also violates the requirements for an anticipatory reference under 35 U.S.C. 102 of the Patent Code. That is, in order for a reference to anticipate a patent claim, the reference must teach each and every element of the claim invention. In this regards, even assuming, for argument sake, that Christianson et al. or Svendsen et al. disclosed corresponding modifications, they would still not anticipate the claimed invention. That is, in order for Christianson to be an anticipatory reference, in addition to adding the specific alterations claimed, you would still also have to change the entire class of enzyme from protease to alpha-amylase. In order to make Svendsen et al. an anticipatory reference, in addition to adding the specific alterations claimed, you would still also have to change the genus from bacterial to fungal and remove Svendsen et al's specific teaching away, namely, that the alterations are based on differences which are not predicted by prior fungal alpha-amylases and bacterial alpha-amylase models build therefrom. Thus, the Examiner's statements or implications about the apparent ease of making Christianson et al. or Svendsen et al. into an anticipatory reference is clearly not correct, and only the Matsuura reference would remotely apply under this hypothetical scenario.

Applicants also respectfully submit that the Examiner's further grounds for maintaining the obviousness rejection are also clearly not valid. The Examiner concedes in the last Office Action that Svendsen et al. is directed to bacterial alpha-amylases which have low homology (the identity is, of course, even lower). The Examiner, however, argues that homology (identity) is not the only factor determining the relatedness of enzymes. In particular, the Examiner

specifically mentions the other factors of physical properties of constituent amino acids of the enzymes, in particular, as predicted from the three-dimensional structure. With respect to the "physical properties of constituent amino acids the enzymes" and the "three dimensional structure", the Examiner has asked Applicants to specifically consider Holm et al. (Protein Engineering, 3(3), 181-191 (1990), which aligns various fungal (Taka-amylase), mammalian and bacterial sources.

Foremost, Applicants agree with the Examiner's statement that other factors are indeed relevant to assess whether changes in one protein can reasonably predict acceptable changes in another protein, including the other factors specifically the Examiner mentioned. However, although agreeing with the Examiner's statement, Applicants add the important additional clarifying information, namely, that homology (identity) is one the most important criteria used in the art to evaluate whether two enzymes are, in fact, related, such that alterations in one enzyme would reasonably be expected to be suitable for another enzyme. Indeed, as is well known in the art, proteins (enzymes) which have a very different amino acid sequences are reasonably expected to behave differently when they are altered in a corresponding fashion, if a corresponding alteration is even possible! This is particularly the case for regions in which there is little or no homology between the sequences. Conversely, proteins which are highly related are reasonably expected to behave similarly when they are altered at a corresponding position.

Nevertheless, even assuming, for the sake of argument, that that the fact that there is very low homology and extremely low identity between the bacterial alpha-amylases of Svendsen et al. and the fungal alpha-amylases of the present invention is not a very important factor (which is clearly not the case), the "other factors" the Examiner mentions, however, actually clearly support the non-obviousness of the claimed invention over the cited art.

In this regard, Applicants have carefully consider Holm et al., and fail to see how Holm et al. establishes that an artisan can reasonably predict suitable alterations in fungal alpha-amylases from the distantly related bacterial alpha-amylases of Svendsen et al.. Holm et al. was an attempt to model build a three-dimensional structure of a bacterial alpha-amylase (which was not available in the art at the time) using a three-dimensional structure of a known fungal alpha-amylase (presumably the next best thing). The resulting 3-D model, however, was based speculation, due to the significant differences between the bacterial alpha-amylases and the fungal alpha-amylases.

Indeed, Holm itself recognizes that the bacterial models which were created based on fungal alpha-amylase were considerably incomplete and based on speculation. The incomplete structure (and subsequent speculation) is evidenced by Holm reporting, e.g., that only six blocks of residues were clearly conserved (see Holm at page 182, col. 2), describing the omission of, e.g., 45 residues and 19 residues segments "due to the lack of a suitable structural template" (see Holm at page 185, col. 1); the need for insertion and deletion or residues (see Holm at page 185); describing the displacement of certain strands (see Holm at page 185, col. 1) and the difficult regions encountered due to the differences (see Holm at page 185, col. 1). Thus, the Examiner implication that the fungal based three-dimensional structure of a bacterial alpha-amylase is reliable for predicting modifications is clearly not correct. Indeed, the reliance on the fungal alpha-amylases to create a model (such as described in Holm et al.) was clearly out of necessity (a lack of a bacterial alpha-amylase model), not out of reliability and confidence in the resulting model.

This point is even also clearly evidenced by Svendsen et al. (which is relied upon by the Examiner for obviousness). In particular, the three-dimensional structure of the bacterial alpha-amylase (which was first provided by Svendsen et al.) turned out to contain, as disclosed in Svendsen et al., some "striking, and not previously predicted structural differences" between fungal and bacterial alpha-amylase. See Svendsen at page 3, lines 5-18. These differences were clearly not revealed in the fungal based bacterial alpha-amylase model (e.g., the model referenced in Holm). Indeed, Svendsen identified a domain that had **"never been seen before in any of the known alpha-amylase"** proteins. See Svendsen et al. at page 11, lines 8-12. Numerous other three-dimensional differences were also identified by Svendsen et al. and were clearly not predicted based on the three-dimensional structure of the bacterial alpha-amylases models prepared from fungal alpha-amylases. (The Examiner implies that because Svendsen et al. mention the Taka amylase at page 2, that the three-dimensional structure Svendsen discloses was model built or based on a fungal alpha-amylase three dimensional structure. This is not correct. Svendsen et al. provided the first reliable three-dimensional structure of a bacterial alpha-amylase, and the three dimensional structure was not based on fungal alpha-amylases, but rather on crystallization of a hybrid bacterial alpha-amylase. See Svendsen at page 9, lines 13-22.) Indeed, only by using a highly related enzyme having sufficient identity and homology was a reliable three dimensional model able to be produced!

Thus, the other factors of physical properties of constituent amino acids of the enzymes, in particular, as predicted from the three-dimensional structure, favors the non-obviousness of

the claimed invention. Indeed, the fact that the fungal and bacterial alpha-amylases share some similarities does not equate to a conclusion that modifications of bacterial alpha-amylases reasonably predict modifications in fungal alpha-amylases, as Svendsen et al. itself establishes that modification in fungal alpha-amylases do not always predict bacterial alpha-amylase which have both different primary amino acid sequence and different three-dimensional structures. Indeed, at best, it can be stated that a modification in a bacterial alpha-amylase *may in some cases* be able to be used to predict modification in fungal alpha-amylases in highly conserved sequences and/or structures. But even this best case is not the case before the Examiner.

In this regard, the Examiner has also clearly failed to give proper consideration, if any, to a clear and unambiguous teaching away in Svendsen et al. that the variants it describes are "based on some striking, and not previously predicted difference between" the Termamyl-like alpha-amylase (bacterial) structure the prior art fungal based three dimensional structures. *See* Svendsen et al. at page 3, lines 6-18. The artisan would clearly interpret this statement in Svendsen et al. to mean that the disclosed alterations are at least not likely applicable to fungal alpha-amylases, such as the enzymes of Matsuura, and thus, the artisan would not have either a motivation or a reasonable expectation of success to modify Matsuura based on Svendsen et al. teachings. *How can an artisan reasonably expect mutations in the bacterial related alpha-amylase of Svendsen et al. to be suitable for fungal related alpha-amylase when the Svendsen et al. specifically teaches that the disclosed mutations were not previously predicted from the fungal based models?*

In sum, the Examiner has clearly not established a *prima facie* case of obviousness, as the Examiner has not established that an artisan would be motivated with a reasonable expectation of success to apply the method of Christianson (which is directed to protease enzymes), to modify the fungal enzyme of Matsuura using the teachings of Svendsen et al. (directed to enzymes which have low homology and extremely low identity to the claimed enzymes and which were not predicted from prior art fungal structures). Moreover, the Examiner has clearly not given proper consideration to the fact that Svendsen et al. specifically teaches away from the claimed invention. *See* MPEP 2142.02 (Prior Art Must Be Considered in Its Entirety Including Disclosures That Teach Away From the Claims) and MPEP 2145 (References cannot be combined where references teaches away from their combination.)

For the foregoing reasons, Applicants submit that the claims clearly overcome this rejection under 35 U.S.C. 103. Applicants respectfully request reconsideration and withdrawal of the rejection.

IV. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

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